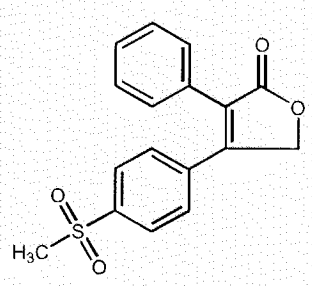
VIOXX®(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX* (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics

* Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25 and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25 mg dose were 3286(±843) ng*hr/mL and 207 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady state conditions are reached by Day 4. The $AUC_{0\text{-}24hr}$ and C_{max} at steady-state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng*hr/mL and 321 (±104) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX Tablets and VIOXX Oral Suspension are bioequivalent.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 µg/mL. The apparent volume of distribution at steady state (V_{dss}) is approximately 91 L following a 12.5 mg dose and 86 L following a 25 mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of rofecoxib, which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see **Drug Interactions**).

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites, and 14% in the feces as unchanged drug.

The plasma clearance after 12.5 and 25 mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e, non-linear elimination). The effective half-life (based on steady state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

VIOXX has not been investigated in patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A pharmacokinetic study in mild (Child-Pugh score $\leq$6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. Limited data in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency suggest a trend towards higher AUC (about 69%) of rofecoxib in these patients, but more data are needed to evaluate pharmacokinetics in these patients. Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not

influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX in these patients.

Drug Interactions

Also see **PRECAUTIONS – Drug Interactions.**

General: In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with rofecoxib have identified potentially significant interactions with rifampin, methotrexate and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal antiinflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found .

CLINICAL STUDIES

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies); this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6 week studies; the diclofenac studies were 12 month studies in which patients could receive additional arthritis medication during the last 6 months.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50 mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Special Studies

Upper Endoscopy in Patients with Osteoarthritis:

Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Heliobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age $\geq$ 65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

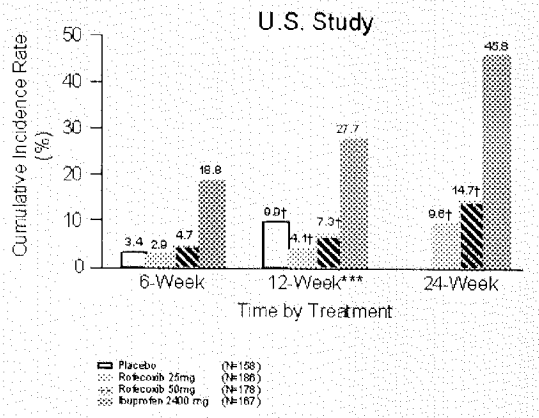
Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo. See Figures 1 and 2 and accompanying Tables for the results of these studies.

208

Figure 1

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm (Intention-to-Treat)**



† p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

209
210
211 **TABLE 1**
212 **Endoscopic Gastroduodenal Ulcers at 12 weeks**
213 **U.S. Study**
214

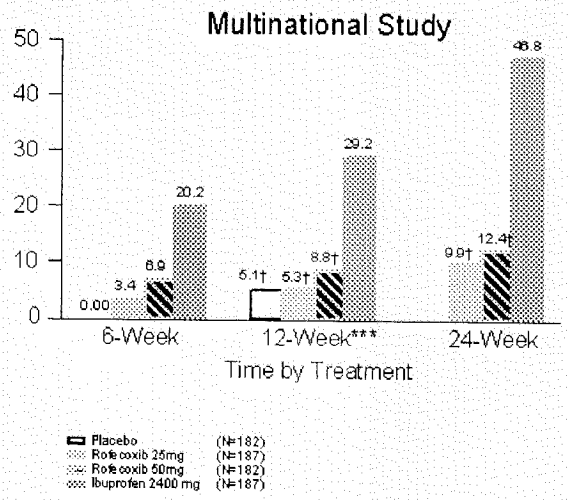
Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	11/158	9.9%	–	–
VIOXX 25 mg	7/186	4.1%	0.41	(0.16, 1.05)
VIOXX 50 mg	12/178	7.3%	0.74	(0.33, 1.64)
Ibuprofen	42/167	27.7%	2.79	(1.47, 5.30)

215 *by life table analysis
216

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm (Intention-to-Treat)**



† $p < 0.001$ versus ibuprofen 2400 mg

** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

TABLE 2
Endoscopic Gastroduodenal Ulcers at 12 weeks
Multinational Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	5/182	5.1%	–	–
VIOXX 25 mg	9/187	5.3%	1.04	(0.36, 3.01)
VIOXX 50 mg	15/182	8.8%	1.73	(0.65, 4.61)
Ibuprofen	49/187	29.2%	5.72	(2.36, 13.89)

*by life table analysis

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS – Gastrointestinal [GI] Effects). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX versus comparator NSAID products have not been performed.

Assessment of Fecal Occult Blood Loss in Healthy Subjects:
Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets:
Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000 mg of VIOXX. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

INDICATIONS AND USAGE

VIOXX is indicated:

For relief of the signs and symptoms of osteoarthritis.

For the management of acute pain in adults (see CLINICAL STUDIES).

For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal,

anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, Special Studies, *Upper Endoscopy in Patients with Osteoarthritis*). Among 3357 patients who received VIOXX in controlled clinical trials of 6 weeks to one year duration (most were enrolled in six month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol derived criteria. Two patients experienced an upper GI bleed within three months (at day 62 and 87 respectively) (0.06%). One additional patient experienced an obstruction within six months (Day 130) and the remaining patient developed an upper GI bleed within 12 months (Day 322) (0.12%). Approximately 23% of these 3357 patients were in studies that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

Anaphylactoid reactions were not reported in patients receiving VIOXX in clinical trials. However, as with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to VIOXX. VIOXX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions,

including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency (see **Pharmacokinetics** – Special Populations). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Renal Effects:
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS.)

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-Advanced Renal Disease).

Hematological Effects:
Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (See CLINICAL STUDIES-Special Studies-Platelets).

Fluid Retention and Edema:

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose, in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma:
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients
VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril,

10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE-inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TXB_2 generation in clotting blood. VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.

Cimetidine: Co-administration with high doses of cimetidine [800 mg twice daily] increased the C_{max} of rofecoxib by 21%, the $AUC_{0\text{-}120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by $AUC_{0\text{-}24\ hr}$ in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in methotrexate renal clearance was observed. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). The effects of the recommended doses for osteoarthritis (12.5 and 25 mg) of VIOXX on plasma methotrexate levels are unknown. Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Warfarin: Prothrombin time (measured as INR) increased in both single and multiple dose cross-over studies in healthy individuals receiving both warfarin and rofecoxib. In a 21 day multiple dose study in healthy individuals stabilized on warfarin (2 to 8.5 mg daily), administration of rofecoxib 25 mg QD was associated with mean increases in INR of approximately 8% (range of INR on warfarin alone, 1.1 to 2.2; range of INR on warfarin plus rofecoxib, 1.2 to 2.4). Somewhat greater mean increases in INR of approximately 11% (range of maximum INR on warfarin alone, 1.5 to 2.7; range of maximum INR on warfarin plus rofecoxib, 1.6 to 4.4) were also seen in a single dose PK screening study using a 30 mg dose of warfarin and 50 mg of rofecoxib. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24}$) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24}$) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the $AUC_{0\text{-}24}$) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24}$).

Pregnancy:

Teratogenic effects: Pregnancy Category C. Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24}$). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24}$). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on $AUC_{0-24)}$.). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery: Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses ≥15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Nursing mothers: Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents approximately 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older. No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

In one of these studies (a six-week, double-blind, randomized clinical trial), VIOXX 12.5 or 25 mg once daily was administered to 174 osteoarthritis patients ≥80 years of age. The safety profile in this elderly population was similar to that of younger patients treated with VIOXX.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6 weeks to 6 months duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

596

Clinical Adverse Experiences occurring in
≥ 2.0% of Patients Treated with VIOXX

	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

The general safety profile of VIOXX 50 mg QD in OA clinical trials up to 6 months (476 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 and 25 mg QD, except for a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema (6.3%) and hypertension (8.2%).

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heart beat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, insect bite reaction

Metabolism And Nutrition: appetite change, hypercholesterolemia, weight gain

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo

Psychiatric Disorder: anxiety, depression, mental acuity decreased

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection

Skin And Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis

Other serious adverse reactions which occur rarely (<0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients taking VIOXX:

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack, unstable angina

Gastrointestinal: colitis, colonic malignant neoplasm, cholecystitis, duodenal ulcer, gastrointestinal bleeding, intestinal obstruction, pancreatitis

Hemic and lymphatic: lymphoma

Urogenital: breast malignant neoplasm, prostatic malignant neoplasm, urolithiasis

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Analgesia, including primary dysmenorrhea

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

In 110 patients treated with VIOXX (average age approximately 65 years) in the post-orthopedic surgery pain study, the most commonly reported adverse experiences were constipation, fever, and nausea.

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of pain has not been studied (See CLINICAL STUDIES, *Analgesia, including primary dysmenorrhea.*)

VIOXX tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

HOW SUPPLIED

No. 3810 – Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-54 unit of use bottles of 90
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3811 – Tablets VIOXX, 25 mg, are yellow, round, tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-54 unit of use bottles of 90
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3784 – Oral Suspension VIOXX, 12.5 mg/5 mL is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3784-64 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 – Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.
NDC 0006-3785-64 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage
VIOXX Tablets:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only.

Distributed by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued Month Year
Printed in USA